Pre Exposure Prophylaxis in HIV

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Faculty Disclosure

- I do not have financial or other relationships with the manufacture(s) of any commercial services discussed in this educational activity.

Objectives

- Identify patients at risk for HIV acquisition who may benefit from pre-exposure prophylaxis (PrEP)
- Describe steps for prescribing PrEP
- Discuss steps to counsel and provide PrEP to patients at high risk for HIV
- Discuss indications to stop PrEP
- Describe what’s up and coming in the pipeline with regard to PrEP.
HIV
- Retrovirus that infects and destroys CD4 cells
- CD4 count: normal range is ~460-1600 cells/mm³
- HIV viral load (VL): goal once patient is on medications is <20 "undetectable"

WHAT IS HIV?
Human Immunodeficiency Virus (HIV) is a virus that attacks cells that help the body fight infection.

There's no cure, but it is treatable with medicine.

Summary of the global HIV epidemic, 2019

- 38.0 million people living with HIV
- 1.7 million new infections
- 0.7 million HIV-related deaths

People living with HIV by WHO region, 2019

- Africa: 38.0 million
- America: 1.2 million
- South-East Asia: 3.7 million
- Europe: 2.8 million
- Eastern Mediterranean: 0.2 million
- Western Pacific: 1.5 million

Source: UNAIDS/WHO estimates
HIV in the US

- At the end of 2017, over 1 million people were living with HIV
- In 2018, there were 37,286 new HIV diagnoses in the US
- Majority of diagnoses were among Black/African American men
- 66% were among gay and bisexual men

New HIV Diagnoses by Age in the US and Dependent Areas, 2018

[Graph showing new HIV diagnoses by age]

Rates of Diagnoses of HIV Infection among Adults and Adolescents

2018—United States and 6 Dependent Areas

N = 37,741 Total Rate = 13.6

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Rate (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-24</td>
<td>15.2</td>
</tr>
<tr>
<td>25-34</td>
<td>13.7</td>
</tr>
<tr>
<td>35-44</td>
<td>12.0</td>
</tr>
<tr>
<td>45-54</td>
<td>10.7</td>
</tr>
<tr>
<td>55-64</td>
<td>9.5</td>
</tr>
<tr>
<td>65+</td>
<td>8.0</td>
</tr>
</tbody>
</table>

Note. Data for the year 2018 are considered preliminary and based on 6 months reporting delay.

Ending the HIV Epidemic: A Plan for America

GOAL:

- 75% reduction in new HIV infections in 5 years
- At least 90% reduction in 10 years.

HHS will work with each community to establish local teams on the ground to tailor and implement strategies to:

- Diagnose all people with HIV as early as possible.
- Treat the infection rapidly and effectively to achieve sustained viral suppression.
- Prevent new HIV transmissions by using proven interventions, including pre-exposure prophylaxis (PrEP) and changes to sexual and injection behaviors.
- Respond quickly to potential HIV outbreaks to get needed prevention and treatment services to people who need them.

[Map of the United States with different states highlighted to show rates of HIV diagnoses]
### National HIV Prevention Objectives on HIV Diagnosis and Care

- Increasing the number of HIV-positive individuals aware of their status to 90%
- Increasing the proportion of persons with newly diagnosed HIV who are linked to care within one month to 85%
- Increasing the proportion of HIV-diagnosed individuals whose virus is effectively suppressed to 80%, with an emphasis on youth and persons who inject drugs

### Globally, 38 Million Are Living With HIV (end of 2019):
Current Status of Achieving Fast Track 2020 Targets for HIV

<table>
<thead>
<tr>
<th>2020 Goals</th>
<th>People Living With HIV</th>
<th>New HIV Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>90% Know Their HIV Status</strong></td>
<td>81%</td>
<td>38.0 million</td>
</tr>
<tr>
<td><strong>90% On HIV Treatment</strong></td>
<td>82%</td>
<td>25.2 million</td>
</tr>
<tr>
<td><strong>90% Are Virally Suppressed</strong></td>
<td>88%</td>
<td>22.2 million</td>
</tr>
<tr>
<td><strong>&lt;500K Annual Diagnoses</strong></td>
<td></td>
<td>1.7 million diagnosed</td>
</tr>
</tbody>
</table>

End of 2019:
- 90% know their status
- 82% on treatment
- 88% virally suppressed
- <500K new diagnoses

### CDC Progression and Transmission of HIV [PATH 2.0] Model 2016

<table>
<thead>
<tr>
<th>Knowledge of HIV Infection</th>
<th>New HIV Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>New</td>
<td>37.5%</td>
</tr>
<tr>
<td>Aware of HIV Infection</td>
<td>83.5%</td>
</tr>
</tbody>
</table>

Source: Li Z, Purcell DW, Sansom SL, Hayes D, Hall

**Continuum of care - United States, 2019: MMWR**
Importance of Routine HIV Screening

- Estimated 1.1 million people in the US are living with HIV
- 1 in 7 do not know they are infected
  - Approximately 38,000 new diagnoses annually
    - 35% of new infections are transmitted by people with undiagnosed HIV
- Risk-based testing strategies fail to identify all who need screening

HIV Prevention
- Blood safety
- Injection safety
- Microbicides
- Prevention of perinatal transmission
- Condom use
- Mutually monogamous sex with a partner who doesn’t have HIV
- Abstinence
- Treatment as Prevention
- Pre-exposure prophylaxis (PrEP)
- Post-exposure prophylaxis (PEP)

What Did We Gain From “Prevention 1.0?”
New HIV Infections – 1980-2010

Pre-exposure Prophylaxis

PrEP IS AN HIV PREVENTION METHOD IN WHICH PEOPLE WHO DO NOT HAVE HIV INFECTION TAKE A PILL DAILY TO REDUCE THEIR RISK OF BECOMING INFECTED

ONLY PEOPLE WHO ARE HIV-NEGATIVE SHOULD USE PrEP. AN HIV TEST IS REQUIRED BEFORE STARTING PrEP AND THEN EVERY 3 MONTHS WHILE TAKING PrEP.

Data Source: Centers for Disease Control and Prevention (2015)
Using Antiretroviral Medications for HIV-1 Prevention

<table>
<thead>
<tr>
<th>Time of transmission</th>
<th>PrEP</th>
<th>PEP</th>
<th>ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to exposure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After infection</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PrEP Trials
Men and Transgender Women Who Have Sex With Men

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Participants</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>Randomized, double-blind, placebo controlled TDF/FTC daily vs placebo</td>
<td>2,499 Peru, Ecuador, Brazil, Thailand, S Africa, U.S.</td>
<td>44% Overall • 75% if took 90% of drug by self report/pill count • 92% if detectable drug level</td>
</tr>
<tr>
<td>IPERGAY</td>
<td>Randomized, double-blind placebo controlled Event driven TDF/FTC</td>
<td>400 France &amp; Canada</td>
<td>86%</td>
</tr>
<tr>
<td>PROUD</td>
<td>Randomized, open label TDF/FTC daily vs placebo • Immediate arm • Delayed arm</td>
<td>544 England</td>
<td>86% in immediate arm</td>
</tr>
</tbody>
</table>

PrEP Trials
Heterosexual Men and Women

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Participants</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partners PrEP</td>
<td>Randomized, double blind placebo controlled Daily TDF or TDF/FTC or placebo</td>
<td>4,758 HIV-discordant couples Kenya &amp; Uganda</td>
<td>75% with TDF/FTC 90% if TDF/FTC detected 67% with TDF</td>
</tr>
<tr>
<td>TDF2</td>
<td>Randomized, double blind placebo controlled Daily TDF/FTC or placebo</td>
<td>1,219 heterosexual men and women Botswana</td>
<td>62%</td>
</tr>
</tbody>
</table>
## PrEP Trials: Women

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Participants</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caprisa 004</td>
<td>Double-blind, randomized, controlled 1% TDF vaginal gel</td>
<td>891 S Africa</td>
<td>34% overall, 54% if high adherence</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>Double-blind, randomized, controlled TDF/FTC or placebo</td>
<td>1981 Aged 18-35 S Africa Kenya Tanzania</td>
<td>Stopped due to lack of efficacy, low adherence</td>
</tr>
<tr>
<td>VOICE</td>
<td>Randomized, double blind TDF or TDF/FTC or TDF gel vs one or topical placebo</td>
<td>5096 Eastern and Southern Africa</td>
<td>Very high self-reported adherence, but low drug levels detected, stopped due to futility</td>
</tr>
<tr>
<td>ASPIRE</td>
<td>Double blind placebo controlled 25 mg dapivirine ring vs placebo</td>
<td>3,629 V Malawi, South Africa, Uganda, and Zimbabwe</td>
<td>27% overall, 61% in women over 25, 10% if younger than 25</td>
</tr>
<tr>
<td>Ring</td>
<td>Double blind placebo controlled 25 mg dapivirine ring vs placebo</td>
<td>1,929 Uganda S Africa</td>
<td>37% overall, 37% if over 21, 10% younger than 21</td>
</tr>
</tbody>
</table>

## PrEP: People Who Inject Drugs

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Participants</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangkok Tenofovir</td>
<td>Double-blind, placebo controlled trial Oral TDF or placebo</td>
<td>2,713</td>
<td>49% 70% in those with detectable plasma TDF level</td>
</tr>
</tbody>
</table>

## HIV prevention pill is not reaching most who could potentially benefit – especially African Americans and Latinos

- 44% of people who could potentially benefit from PrEP (approx. 500,000 people) were prescribed PrEP
- 25% of people who could potentially benefit from PrEP (approx. 500,000 people) were prescribed PrEP
Potential Benefits of PrEP

- Prevent HIV transmission
- Bring more attention to sexual health – proactive / taking control
- Can help resolve “discordance dilemma”
- Decreased anxiety, increased communication,
- Increased disclosure
- Increased trust
- Increased self-efficacy
- Increased sexual pleasure
- Increased intimacy

2 FDA-Approved Medications for PrEP

Each consists of two drugs combined in a single oral tablet taken daily
1. Emtricitabine (F) 200 mg combined with tenofovir disoproxil fumarate (TDF) 300 mg (F/TDF – brand name Truvada®)
2. Emtricitabine (F) 200 mg combined with tenofovir alafenamide (TAF) 25 mg (F/TAF – brand name Descovy®)

Approved to prevent HIV infection in adults and adolescents weighing at least 77 pounds (35 kg)

FDA Indications for F/TDF vs F/TAF

- F/TDF (Truvada®)
  - Prevention of HIV infection among all people at risk through sex or injection drug use
  - Renal function: eGFR > 60 mL/min
- F/TAF (Descovy®)
  - Prevention of HIV infection among people at risk through sex, excluding people at risk through receptive vaginal sex
  - Renal function: eGFR > 30 mL/min
Truvada® (F/TDF)
- Approved for HIV PrEP in 2012
- One pill by mouth daily with or without food
- Do not use for PrEP if estimated eGFR < 60 mL/min
- Potential side effects
  - Headache, nausea, flatulence – usually resolves in 2-4 weeks
  - Decreased bone mineral density (no fracture risk)
  - Renal dysfunction including Fanconi syndrome
  - Lactic acidosis; hepatomegaly with steatosis

Descovy® (F/TAF)
- Approved for HIV PrEP for prevention of sexual transmission, excluding individuals at risk from receptive vaginal sex on October 3, 2019
- One pill by mouth daily with or without food
- Do not use if estimated eGFR < 30 mL/min
- Potential side effects
  - Headache, nausea, flatulence – usually resolves in 2-4 weeks
  - Decreased bone mineral density (no fracture risk)
  - Renal dysfunction including Fanconi syndrome
  - Lactic acidosis; hepatomegaly with steatosis
  - Typically reversible with stopping Descovy®

Which medication should I prescribe for daily PrEP?
Comprehensive HIV Prevention
PrEP is always part of a comprehensive HIV prevention package
- Condoms
- Counseling
- Frequent STD testing and treatment
- Frequent HIV testing

PrEP Steps
- Risk assessment
- Eligibility evaluation
- Monitoring
- Evaluation for indication to stop PrEP

Taking a Sexual History
- Make it a normal part of each visit
- The Five “P”s
  - Partners
  - Practices
  - Protection from STDs
  - Past history of STDs
  - Prevention of pregnancy

Who Should be Offered PrEP?


All AI recommendations

<table>
<thead>
<tr>
<th>Man Who Have Sex with Men</th>
<th>Heterosexual Women and Men</th>
<th>Persons Who Inject Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-positive sexual partner</td>
<td>HIV-positive sexual partner</td>
<td>HIV-positive injecting partner</td>
</tr>
<tr>
<td>Recurrent bacterial STI</td>
<td>Recent bacterial STI</td>
<td>Sharing injection equipment</td>
</tr>
<tr>
<td>High number of sex partners</td>
<td>History of treatment or infection</td>
<td></td>
</tr>
<tr>
<td>History of insecure or inconsistent use</td>
<td>Shared use of equipment</td>
<td></td>
</tr>
<tr>
<td>Commercial sex work</td>
<td>in high HIV prevalence area or network</td>
<td></td>
</tr>
</tbody>
</table>

Step 2: Eligibility

Eligibility

- Negative HIV test
- No signs/symptoms of acute HIV infection*
- Normal renal function
- HBV infection & vaccination status
  - TDF/FTC treats HBV
  - Risk for worsening of HBV infection with discontinuation
Baseline Lab Evaluation

- Negative HIV test – 4th generation test
- Screen for bacterial STDs: urine, oral or anal swab and RPR
- Serologic screen for Hepatitis B
  - Vaccinate if nonimmune
- Serologic screen for Hepatitis C
  - Consider annual screening for MSM, intravenous drug users
- Expert recommendation
  - Serologic screen for Hepatitis A if MSM
  - Immunize if negative
- Creatinine clearance > 60 mL/min
- UA or dipstick for urine proteinuria
- Pregnancy test

Hepatitis B and PrEP

- Check hepatitis B serology before initiating PrEP
- Severe acute exacerbations of hepatitis B can occur in patients infected with hepatitis B who discontinue current PrEP medications
- Vaccinate if nonimmune
Step 3: Follow Up

Prescribe PrEP if Indicated

- Daily TDF/FTC (Truvada®)
- Daily TAF/FTC (Descovey®) only for (male or transwomen)
- ≤ 90 day supply

Prescribing and Monitoring

- One tablet daily every day with or without food
- Time to achieving protection (adequate tissue levels of tenofovir diphosphate) may depend on site of exposure:
  - 20 days for blood mononuclear cells and cervicovaginal tissues
  - 7 days for rectal tissue
- However, these levels may not represent true clinical protection
  - Guidelines do not provide specific recommendations on time to protection
  - Critical to counsel on safer sex practices in combination with P/EP

Adherence Is Critical

![Graph showing adherence rates over time.

Lab Test Every 3 months At least every 6 months Considerations

<table>
<thead>
<tr>
<th>Lab Test</th>
<th>Every 3 months</th>
<th>At least every 6 months</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Ab</td>
<td>X</td>
<td></td>
<td>Consider HIV RNA PCR</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td></td>
<td>Check CMP or serum creatinine + UA</td>
<td></td>
</tr>
<tr>
<td>STD screen</td>
<td>X</td>
<td>RPR every 6 months</td>
<td>Test at site of exposure</td>
</tr>
<tr>
<td>Pregnancy test for women</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


WHAT ARE RISKS OF PREP
**PrEP (TDF/FTC): Side Effects**

- Headache
- Abdominal pain
- Poor appetite/weight loss
- “start-up syndrome”
- Renal impairment, Fanconi syndrome
- Lactic acidosis
- Severe hepatomegaly/steatosis
- HBV exacerbation in those with chronic hepatitis B infection (if discontinued)

**What are the Common Side Effects of PrEP?**

- 9% nausea / stomach upset*
- 4.5% headaches*
- <1% kidney issues
- Decrease in bone mineral density

* these usually get better after the first few weeks

**Renal Effects and Monitoring**

- Estimated creatinine clearance (eCrCl) should be assessed prior to starting Truvada® for PrEP, reassessed at 3 months and then every 6 months
- Truvada® for PrEP should not be used if CrCl is < 60 mL/min
- If a patient is at risk for renal impairment, then CrCl, serum phosphorus, urine glucose, and urine protein should be monitored before and during Truvada® for PrEP use
Effect of PrEP Medication on Bone Density
Changes in bone mineral density (BMD) and mineralization problems have been noted in those taking TDF
- Assess BMD in patients with history of pathologic fractures and/or risk for osteoporosis or bone loss
- Monitor for persistent and/or worsening bone pain, fractures, and/or muscle weakness

Development of Resistance
- Risk is low despite 2 drug therapy with PrEP
- IPrEx
  - 48 people with HIV – none with significant resistance
- Partner’s PrEP
  - 5 of 63 seroconverters developed resistance
  - M184V

What if the HIV test is positive?
- Do confirmatory test if rapid test positive
- Convert the PrEP regimen to an HIV treatment regimen recommended by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents
  - Continue Truvada and add either dolutegravir 50 mg PO once daily or darunavir 800 mg with ritonavir 100 mg once daily
- Order an HIV-1 RNA PCR, HIV-1 Genotype, CD4 count and other baseline labs
- Reinforce need for adherence to medications
- Discuss the importance of condom use to protect sex partners and provide condoms
- Offer HIV testing for sex and drug injection partners, nPEP and assistance with disclosure
- Link to an experienced HIV provider

Discontinuing PrEP

- Positive HIV result
- Acute HIV signs or symptoms
- Non-adherence
- Renal disease
- Changed life situation: lower HIV risk
- Document HIV status at time of discontinuation, reason for discontinuation

PrEP May Be Periodic

PrEP in Pregnancy

- The antivirals used for PrEP are widely used for the treatment of HIV infection and continued during pregnancies that occur.
- The data on pregnancy outcomes in the Antiretroviral Pregnancy Registry provide no evidence of adverse effects among fetuses exposed to these medications
- Both the FDA documentation and the perinatal antiretroviral treatment guidelines permit off-label use in pregnancy.
- Providers should discuss available information about potential risks and benefits of beginning or continuing PrEP during pregnancy so that an informed decision can be made.
Does PrEP promote risky behavior?

Risk Compensation
- Increased risky behavior if people think they are protected
- Risk compensation after PrEP studied in several trials and no evidence of increased risky behavior or STD's found
- iPrEx: no changes in reported sexual practices from baseline and no increase in STD's

PrEP in Clinical Practice: What Are the Barriers to PrEP Uptake?
- Users
  - Unaware of HIV risk, PrEP availability, or how to access it
  - No or delayed access to clinical preventive care
  - Lack of knowledge about insurance coverage
  - Adherence challenges
  - Concern about disclosure and stigma
- Providers
  - Unaware of intervention
  - Wary of complexity and time involved
  - Discomfort with assessing risk
  - Uncertain how to bill for intervention
Insurance

- PrEP cost is around $13,000/year
- Assistance for those with and without insurance

PrEP Patient Assistance

- Uninsured patients
  - Gilead’s Medication Assistance Program
    - 1-855-330-5479
    - http://start.rtuvada.com/content/pdf/medication Assistance Program.pdf
  - Partnership for Prescription Assistance (PPA) Program
    - 1-888-477-2669
    - www.pparx.org

- Patients with Insurance
  - Gilead Co-pay Coupon Card
    - www.gileadcopay.com
    - 1-877-505-6986
  - Patient Access Network Foundation
    - www.panfoundation.org/hiv-treatment-and-prevention
Ready, Set, PrEP

- Launched by the US Department of Health and Human Services on 12/3/19
- To qualify, patients must:
  - test negative for HIV
  - have a valid prescription from a healthcare provider
  - not have prescription drug coverage
- Beginning no later than March 30, 2020, patients may obtain PrEP through CVS, Walgreens, Rite Aid or mail order all at no cost
- https://www.getyourprep.com/ or 855-447-8410
- HIV.gov Locator

“On-Demand” PrEP

- IPERGAY trial found that taking PrEP on a 2-1-1 schedule reduced risk of HIV infection by 86% in MSM
- HPTN 083- PrEP with IM CAB vs TDF/FTC
  - Phase 3 randomized double blinded HIV PrEP international study
  - Study population: High risk adult MSM/TGW (n=4750)
  - Study population: 67% 30 years
  - 12% TGW
  - Cabotegravir: Oral lead in 5 weeks ->IM q2 months vs TDF/FTC po daily
HPTN 083- PrEP with IM CAB vs TDF/FTC

- Results:
  - DSMB stopped study early
  - New HIV infections: 13 (CAB) vs 39 (TDF/FTC)
  - HIV incidence: 0.41 (CAB) vs 1.22 (TDF/FTC)

Conclusion: CAB non inferior and superior.

The PARTNER1 study looked at 888 couples where one was HIV positive and on antiretroviral treatment (ART) and who were already having sex without condoms:
- 548 heterosexual couples
- 340 MSM

- They found that in more than 58,000 acts of condomless sex there were no HIV transmissions from the HIV positive partner among those on treatment with an undetectable viral load.
- Couples were followed for a median of 1.3 years.

Partner2 Study:
- Prospective observational study in 14 European countries
- Enrolled 927 homosexual serodiscordant couples between September 2010 and July 2017
- Positive partner was on suppressive ART
- A total of 74568 condomless-sex acts were reported, with 0 cases of within couple HIV transmission.

http://programme.aids2018.org/Abstract/Abstract/13470
Conclusions/Recommendations

- PrEP Works!
- Most efficacious if we coordinate our efforts in the community
- We all have a role to play: public health officials, community activists, educators, providers.
- Don’t forget other pillars of prevention:
  - HIV Testing that adheres to CDC/USPTF guidelines
  - Treatment as Prevention
  - PEP
- Provider education and buy-in is key
- Raise awareness in the community to increase uptake and reduce stigma

Have the Discussion

http://betablog.org/new-resource-prep-right-for-me/
Resources

- http://www.truvadapreprems.com/
- https://aidsinfo.nih.gov/
- http://www.cdc.gov/hiv/prevention/research/prep/
- http://www.avac.org/

Educational Materials: Pamphlets

Medical Team’s PrEP Resources
Questions?

THANK YOU!